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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/903,216	Wands et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *16-22 and 39-56* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *16-22, 39-46, and 49-56* is/are rejected.

7) ☒ Claim(s) *47 and 48* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicants election without traverse of Group I, drawn to methods of inhibiting tumor growth in a mammal comprising the administration of compounds which inhibit the enzymatic activity of HAAH.

2. Claim 37 is canceled. Claims 16-22 and 39-56 are pending and examined on the merits.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification

4. The disclosure is objected to because of the following informalities:

(A) The specification is objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. The specification contains numerous recitations of HAAH. One species of HAAH is identified in Table 1 as SEQ ID NO:2, encoded by SEQ ID NO:3 (Table 2). The specification refers to other species of HAAH encoded by cDNAs in Table 4 (page 47). When

the specification of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. Without a sequence identifier, it is unclear if a reference to HAAH in the specification is synonymous with SEQ ID NO:2. Appropriate correction is required.

(B) Page 6, line 16 contains a blank space after "SEQ ID NO".

Appropriate correction is required.

Claim Objections

5. Claims 16-22, 39-44 and 49-56 are objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. Claims 16, 18-20, 39, 40 and 44 recite "HAAH". Table 1 identified HAAH as SEQ ID NO:2. When the claims of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. Appropriate correction is required.

6. Claims 47 and 48 are objected to as bieng dependent upon a rejected base claim.

Claim Rejections - 35 USC § 112

7.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 16-22, 39-44 and 49-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are rended vague and indefinite by recitation of "HAAH" as the only means of identifying the protein to which the claimed antibodies bind. The use of laboratory designations only to identify a particular protein renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct proteins. Amendment of the claims to incorporate a sequence identifier would overcome this rejection.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to provide an enabling disclosure without complete evidence either that the claimed biological materials are know and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the hybridoma cell line producing the monoclonal antibody designated FB50. Exact replication of a cell line is an unpredictable event. Clark (Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man, 1993, page 1) states "The in vivo antibody response is heterogeneous and is made up of a large mixture of antibodies secreted from a polyclonal population of cells. In addition, because the differentiation of B cells involves the random rearrangements of gene segments and somatic mutation of these rearranged genes,....no two animals, even of an inbred strain will make an identical set of antibodies." Although the applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive an antibody identical to FB50. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtained the claimed antibody..

Although FB50 is known in the art through publication by a member of the instant inventive entity, the M.P.E.P. (2403) states:

> The mere reference to a deposit or the biological material itself in any document or publication does not necessarily mean that the deposited biological material is readily available. Even a deposit made under the Budapest Treaty and referenced in a United States or foreign patent document would not necessarily meet the test for known and readily available unless the deposit was made under conditions that are consistent with those specified in these rules, including the provision that requires, with one possible exception (37 CFR 1.808(b)), that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent. Ex parte Hildebrand, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990).

Thus, in order to satisfy the requirements of 35 U.S.C. 112, first paragraph, a deposit of FB50 is required.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposit has been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited hybridoma is producing the monoclonal antibody FB50 as described in the specification as filed and is the same as that deposited in the depository, stating that the deposited hybridoma is producing the identical monoclonal antibody of FB50 as described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

11. Claims 16, 17, 39, 40, 41, 49-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting tumor growth in a mammal comprising the administration of an antibody conjugated to a chemotherapeutic agent or an antibody capable of eliciting antibody dependent cytotoxicity (ADCC) or complement dependent (CDCC), does not reasonably provide enablement for a method of inhibiting tumor growth in a mammal comprising the administration of an antibody or an intrabody which binds the intracellular catalytic domain of HAAH. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 16 is drawn to a method of inhibiting tumor growth in a mammal comprising the administration of a compound which inhibits an enzymatic activity of HAAH. Claim 16 specifically recites hydroxylase activity. Claim 20 embodies the method of claim 16, wherein said compound is an intrabody. Claim 39 embodies the method of claim 16, wherein said compound is n antibody or fragment thereof that specifically binds to HAAH. Claim 40 specifies that the epitope is within the catalytic domain of HAAH. It is noted that although the art teaches that the epitope for FB50 is accessible on the cell surface when over expressed (page 1320, first column, lines 1-8 of Lavaissiere et al, Journal of Clinical Investigation, 1996, Vol. 98, pp. 1313-1323), the epitope is not within the catalytic domain of HAAH. Jia et al (PNAS, 1994, Vol. 91, pp. 7227-7231) identify the catalytic domain of bovine HAAH a consisting of a his-2 motif between residues 675 and 692 (Figure 2 of Jia et al). Korioth et al (Gene, 1994, Vol. 150, pp. 395-399) disclose the amino acid sequence for human HAAH and compared it to bovine HAAH (Figure 5 of Korith et al). Korith et al note that the C-terminal region consisting of residues 310-757 is highly conserved between bovine and human HAAH (page 398, first column, under the heading of "Comparison of the deduced sequences"). One can conclude by this comparison that the his-2 motif in human HAAH includes residues 678 to 695, and thus the catalytic domain consists of residues 678 to 695 of human HAAH.. Lavaissiere et al teach that the amino acid residues obtained by immunoscreening with the FB50 antibody are residues 146 to 183 (see Figure 4 and

legend regarding the amino acids obtained by immunoscreening). Thus it can be concluded that FB50 does not bind to the catalytic domain of human HAAH. The specification teaches a number of monoclonal antibodies which are useful for binding to an epitope of the HAAH polypeptide which is exposed on the surface of the cell (pg 2, lines 25-29) including the FB50 antibody.. The specification briefly discusses the basic principles of an intrabody (pg 2-3, lines 30-4). However, the specification does not disclose a specific intrabody, by amino acid sequence, or by deposit, that would act to efficiently bind the HAAH polypeptide endogenously and thereby inhibit the growth of a tumor in vivo. In order to produce intrabodies the nucleic acid sequences, of minimally the complimentary determining region, are necessary (Jones et al., Advanced Drug Delivery Reviews 1998, page 154, column 1, lines 18-26, and page 160, lines 24-25). The specification clearly fails to describe the nucleic acid sequences of an entire intrabody let alone the necessary complimentary determining regions. An intrabody by definition is an antibody that is expressed inside of a cell as a therapeutic agent. In order to get expression of an intrabody, especially in cells of the central nervous system an efficient means of transferring the genes is necessary. Clearly, the specification fails to describe the necessary delivery vehicles for the insertion and expression of an intrabody.

12. Claims 16, 17, 52, 55 and 56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating non-central nervous system tumors by means of an antisense construct to HAAH, does not reasonably provide enablement for a

method of treating a central nervous system tumor comprising the administration of an antisense construct to HAAH.. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is well know in the art that the use of modified anti-sense oligonucleotides on CNS targets are limited by the powerful ability of the blood-brain barrier to exclude such anti-sense oligonucleotide. In order to use anti-sense technology for treatment of CNS pathologies, careful consideration must be made with respect to the target nucleotide sequence within the gene of interest, the choice of backbone modifications for the oligonucleotide, and the presence of special sequence motifs which predispose the oligonucleotide to undesirable non-antisense effects (Broaddus et al, Methods in Enzymology, 2000, Vol. 314, pp. 121-135). The published data indicates that only a small percentage of the antisense oligonucleotides which are tested in vitro are actually effective in the reduction of the target mRNA, and that the ability of the anti-sense oligonucleotides to bind to a target mRNA cannot be predicted due to the structure and conformation assumed by individual mRNA specie (Broaddus et al, pg. 122). Further, even if the specific structure and conformation of a particular mRNA could be adequately predicted as an isolated molecule in a protein-free environment, it would not anticipate the accessible sites for the anti-sense oligonucleotide in vivo, wherein proteins are available to bind to the mRNA thus obscuring the oligonucleotide binding sites and potentially altering the conformation of the target mRNA. Broaddus et al teaches that a highly empirical approach to the testing of candidate anti-

sense oligonucleotides is critical for the establishment of an antisense oligonucleotide as a therapeutic agent for the treatment of patients. This requirement has not been met by the instant specification, therefore, one of skill in the art would be forced into undue experimentation without reasonable expectation of success in order to practice the invention as claimed.

13. Claims 16-22, 39-44, 49-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant specification provides a written description of the protein of SEQ ID NO:2 encoded by the cDNA of SEQ ID NO:3. The protein is identified as a human Aspartyl(Asparaginyl) beta Hydroxylase. The specification sets forth SEQ ID NO:2 as HAAH but does not always refer to HAAH as SEQ ID NO:2. When given the broadest reasonable interpretation, the claims drawn to HAAH embody allelic and splice variants as well as fragments of HAAH formed from post-translational cleavage. For example, is known in the art that HAAH undergoes post translational cleavage to produce a smaller protein (Radosevitch, U.S. 6,166,176, column 3, lines 1-10) but there is no written description of the fragment produced thereby. Further, the claims do not limit HAAH by function or specific hydroxylation activity, as claim 1 is drawn to limiting an enzymatic activity, rather than hydroxylation.. Claim 9 is drawn to a catalytic domain. The specification disclose only one catalytic domain for HAAH in Table 1, said catalytic

domain responsible for the hydroxylation activity of SEQ ID NO:2. No other catalytic site are described by the specification or any art of record. Thus the claims are based on a genus of HAAH which is highly variant and catalytic domains beyond the hydroxylation domain consisting of residues 678-695 which are undisclosed. The specification provides a written description of SEQ ID NO:2 and the catalytic site at residues 678-695 responsible for hydroxylation activity, and this is inadequate to support claims to a genus of HAAH molecules or any alternative catalytic domain. The nature of protein variants produced by allelic sequences, splice variants or post-translational processing is that they are variant structure where the structure and function of one example does not provide guidance to the structure and function of the other members of the genus and the specification provides no teachings to describe any other members of the genus. According to these facts one of skill in the art would conclude that the applicant was not in possession of the claimed genus because a description of only one member of this genus, SEQ ID NO:2, is not representative of the variants of the genus and is therefore insufficient to support the claims.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 16, 17 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by DeWys et al (Cancer chemotherapy Reports, 1973, Part 1, Vol. 57, pp. 41-49 as evidenced by Hanauske-Abel et al (U.S. 5,789,426).

Claims 16 and 17 are drawn to the inhibition of tumor growth comprising the administration of a compound that inhibits the hydroxylase activity of HAAH. Claim 21 embodies the method of claim 16 wherein the compound is L-mimosine.

DeWys et al disclose a method of inhibiting the growth of tumor cells in mice comprising the administration of Mimosine (abstract).

Hanauske-Abel et al discloses that L-mimosine is an inhibitor of hydroxylation (column 4, lines 41-43). Thus it is inherent in the method of DeWys et al that the hydroxylation activity of HAAH is inhibited.

16. Claims 16, 17 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Fujii (EP 180,188).

Claims 16 and 17 are drawn to the inhibition of tumor growth comprising the administration of a compound that inhibits the hydroxylase activity of HAAH. Claim 22 embodies the method of claim 16 wherein the compound is hydroxypyridone.

Fujii discloses a method of inhibiting tumor growth in a mammal comprising the administration of a composition comprising a hydroxypyridone (page 2, line 1 to line 56).

Fujii discloses a method of inhibiting the growth of tumor cells in a mammal comprising the administration it is inherent in the method of DeWys et al that the hydroxylation activity of HAAH is inhibited.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 16, 17, 39 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular

Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134) in view of Sinkule et al (Tumour Biology, 1991, Vol. 12, pp. 198-206) and Radosevitch (U.S. 6,166,176, reference A1 of the I.D.S. filed November 21, 2001).

Claims 16 and 17 are drawn to the inhibition of tumor growth comprising the administration of a compound that inhibits the hydroxylase activity of HAAH. Claim 39 is drawn to the method of claim 16 wherein said compound is an antibody or fragment thereof. Claim 41 embodies the method of claim 16, wherein said compound is a single chain Fv molecule.

Schlom et al teaches a method for inhibiting tumor growth in a mammal comprising the administration of antibodies conjugated to chemotherapeutic drugs. Schlom teaches the advantages of single chain antibodies over the parent murine antibodies comprise rapid clearance from the blood and body to avoid unwanted by-stander tissue toxicity, reduced accumulation in the kidneys, especially for the avoidance of renal toxicity associated with drug conjugated antibodies, increased penetration of tumor masses, reduced immunogenicity due to lack of antibody effector domains (page 122, second column, lines 2-23) as well as relative ease of production (lines 27-30). Schlom does not teach antibodies which bind to HAAH, or Labrythin or antibodies which inhibit hydroxylation.

Sinkule et al teach the immunoconjugate consisting of monoclonal antibody 44-3A6 conjugated to doxorubicin which exhibits specific toxicity in vitro against a tumor cell line expressing the A549 antigen to which said antibody binds (Table 2, especially lines 3 and 5).

Radosevitch et al teach the monoclonal antibody 44-3A6 which reacts with a cell surface antigen on a human lung carcinoma cell line, A549. Radosevich et al tach that the Lab antigen is frequently expressed by tumors, is expressed by all cells of a given cancer at all times and is infrequently expressed by normal cells. Radosevitch ('176) teach that this antibody binds to an epitope from residues 117-123 of Labyrinthin, which has an identical domain with HAAH (figure 3). Residues 117-123 in Labyrinthin are residues 175-181 of HAAH.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the immunoconjugate taught by Sinkule et al in the method of inhibiting tumor growth in a mammal by the administration of antibodies and fragments thereof conjugated to chemotherapeutic agents as taught by Schlom. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Radosevitch on the selectivity of tumor cells versus normal cells in the expression of the Lab antigen on the cell surface. It would be inherent in this method that the administered immunoconjugate of Sinkule would bind to HAAH as Radosevitch et al teach that the 44-3A6 monoclonal antibody binds to an epitope from residues 117-123 of Labyrinthin, which has an identical domain with HAAH (figure 3) and residues 117-123 in Labyrinthin are residues 175-181 of HAAH. Furthermore, the killing of cells by the binding of administered immunoconjugate would inherently result in inhibition of hydroxylation activity by killing the cells that were expressing HAAH.

19. Claims 16, 17, 39, 41, 42, 43, 51 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134) in view of Lavaissiere et al (Journal of Clinical Investigation, 1996, Vol. 98, pp. 1313-1323, reference C19 of the I.D.S. submitted November 21, 2001). The embodiments of claims 16, 17, 39 and 41 are set forth above. Claim 42 is drawn to the method of claim 16 wherein said compound is a FB50 antibody. Claim 43 is drawn to the method of claim 16 wherein said compound is a FB50 single chain antibody. Claim 51 embodies the method of claim 16 wherein said tumor is selected from the group comprising breast cancer, liver cancer, and cancer of the bile ducts. Claims 53 and 54 specify hepatocellular carcinoma and chlolangiocarcinoma, respectively.

Schlom et al teaches a method for inhibiting tumor growth in a mammal comprising the administration of antibodies conjugated to chemotherapeutic drugs (page 107) or radio nuclides. (page 108). Schlom teaches the advantages of single chain antibodies over the parent murine antibodies comprise rapid clearance from the blood and body to avoid unwanted by-stander tissue toxicity, reduced accumulation in the kidneys, especially for the avoidance of renal toxicity associated with drug conjugated antibodies, increased penetration of tumor masses, reduced immunogenicity due to lack of antibody effector domains (page 122, second column, lines 2-23) as well as relative ease of production (lines 27-30). Schlom does not teach antibodies which bind to HAAH, or antibodies which inhibit hydroxylation.

Lavaissiere et al disclose the monoclonal antibody FB-50 which binds to HAAH (page 1316, second column, under the heading "Molecular cloning of the antigen: its identification as HAAH". Lavaissiere et al disclose that the epitope recognized by FB-50 is on the cell surface (page 1320, first column, lines 1-5) and is present in hepatocellular carcinoma and chlolangiocarcinoma, breast and colon carcinomas (Table 1) thus fulfilling the specific embodiments of claim 52 with respect to cancer of the liver, bile ducts, breast and colon. Lavaissiere et al teach that HAAH is responsible for an increase in hydroxylation activity in cancer cells which over express HAAH (Figure 7).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the FB50 antibody as taught by Lavaissere et al in the method of inhibiting tumor growth in a mammal by the administration of antibodies and fragments thereof conjugated to chemotherapeutic agents or radio nuclides as taught by Schlom. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Lavaissere et al on the expression of the FB50 epitope in hepatocellular carcinomas, cholangiocarcinomas, breast and colon cancers in contrast to its low expression in normal hepatocytes and non-neoplastic epithelial cells (abstract).. It would be inherent in this method that the administered immunoconjugate or radioconjugate of would result in inhibition of hydroxylation activity by killing the cells that were expressing HAAH.

20. Claims 16, 17, 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dietz (U.S. 5,814,500) in view of Radosevich (U.S. 6,166,176, reference A1 of the I.D.S. filed November 21, 2001). The embodiments of the claims are set forth above.

Dietz teaches general methods of inhibiting tumor growth in a mammal comprising the delivery of antisense constructs to inhibit the expression of targeted genes. Dietz do not teach compounds comprising antisense nucleic acid which inhibit HAAH or hydroxylation activity.

Radosevich discloses that the protein coding region of the Labyrinthin gene comprises the protein coding region of the HAAH gene (column 7, lines 7-11). Radosevich discloses the use of the full-length antisense Labyrinthin cDNA to reduce the growth rate of A549 cells (column 9, second paragraph), which are tumor cells derived from a hepatocellular carcinoma. Radosevich et al tach that the Lab antigen is frequently expressed by tumors, is expressed by all cells of a given cancer at all times and is infrequently expressed by normal cells. Radosevitch et al disclose that the protein coding region of Labyrinthin has about 99.6% homology with an internal segment of the protein coding region for HAAH (column 6, lines 65-67).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the antisense nucleic acid of Radosevitch to a mammal having hepatocellular carcinoma. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Radosevich et al on the increased expression of the Lab antigen in hepatocellular carcinoma cells. The full length

antisense Labyrinthin cDNA would inherently hybridize to the mRNA for HAAH and inherently inhibit the expression of HAAH and the resulting hydroxylase activity thereof.

21. Claims 16, 17-19, 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ullrich et al (U.S. 5,851,999) in view of Jia et al (PNAS, 1994, Vol. 91, pp. 7227-7231) and Korioth et al (Gene, 1994, Vol. 150, pp. 395-399) and Lavaissiere et al (Journal of Clinical Investigation, 1996, Vol. 98, pp. 1313-1323, reference C19 of the I.D.S. submitted November 21, 2001). The embodiments of claims 16 and 17 are set forth above. Claim 18 embodies the method of claim 16, wherein said compound is a dominant negative mutant of HAAH. Claim 19 specifies that the mutant comprises a mutation in the catalytic domain of HAAH. Claim 44 specifies that said mutation comprises a substitution or deletion of a histidine residue in said catalytic domain. Claim 45 embodies the method of claim 19 wherein said mutation is located between residues 650 and 700 of SEO ID NO:2. Claim 46 specifies the residue at position 675.

Ullrich et al teach a method of inhibiting tumor growth in a mammal comprising the administration of a dominant-negative mutant of VEGF (column 5, lines 39-64, and column 19, line 25 to column 20, line 23). Ullrich et al teach the administration of pharmaceutical compositions comprising FLK-1 receptor modulating compounds directly to the tumor as well a systemically (column 23, line 39 to column 24, line 15), thus fulfilling the specific embodiments of claims 49 and 50. Ullrich do not teach the administration of dominant negative mutants of HAAH or compounds which inhibit hydroxylation activity.

Lavaissiere et al teach that HAAH is responsible for an increase in hydroxylation activity in cancer cells which over express HAAH (Figure 7). Lavaissiere et al disclose that an epitope of HAAH is present in hepatocellular carcinoma and cholangiocarcinoma, breast and colon carcinomas (Table 1) thus fulfilling the specific embodiments of claim 52 with respect to cancer of the liver, bile ducts, breast and colon. Lavaissiere et al teach that HAAH is responsible for an increase in hydroxylation activity in cancer cells which over express HAAH (Figure 7). Lavaissiere et al teach that it is necessary to establish whether the substantially increased activity of HAAH is merely associative or contributes to the generation and maintenance of the malignant phenotype (page 1322, last sentence).

Jia et al (PNAS, 1994, Vol. 91, pp. 7227-7231) identify the catalytic domain of bovine HAAH a consisting of a his-2 motif between residues 675 and 692 (Figure 2 of Jia et al). Korioth et al (Gene, 1994, Vol. 150, pp. 395-399) disclose the amino acid sequence for human HAAH and compared it to bovine HAAH (Figure 5 of Korith et al). Korith et al note that the C-terminal region consisting of residues 310-757 is highly conserved between bovine and human HAAH (page 398, first column, under the heading of "Comparison of the deduced sequences"). One can conclude by this comparison that the his-2 motif in human HAAH includes the same residues and thus the catalytic domain consists of residues 675 to 692 of human HAAH. Jia et al teach that when the his-675 residue was mutated to an alanine, no hydroxylation activity was detected in the resulting mutant This residue corresponds to a histidine residue in human HAAH as evidenced by Korith et al.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a the dominant negative mutant of HAAH by substitution the his-675 residue with alanine, and administer said mutant to a mammal to inhibit tumor growth. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Jia et al and Korith et al on the necessity for the His-675 residue for hydroxylation activity in HAAH and the suggestion of Lavaissiere et al on the need to establish the associative or casual nature of the increased hydroxylation activity by HAAH in carcinoma cells.

Conclusion

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Patent Examiner, Group 1642

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